DOI:
10.1080/07853890.2018.1530450

Document Version
Peer reviewed version

Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: http://www.tandfonline.com/loi/iann20

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To cite this article: Bashir Alaour, Felicity Liew & Thomas E Kaier (2018): Cardiac Troponin - Diagnostic Problems and Impact on Cardiovascular Disease, Annals of Medicine, DOI: 10.1080/07853890.2018.1530450

To link to this article: https://doi.org/10.1080/07853890.2018.1530450

Accepted author version posted online: 28 Sep 2018.

Cardiac Troponin - Diagnostic Problems and Impact on Cardiovascular Disease

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Cardiac Troponin - Diagnostic Problems and Impact on Cardiovascular Disease

The definition of a high-sensitivity cardiac Troponin (cTn) assay describes the ability to quantify a cardiac biomarker level in at least 50% of healthy individuals. This advance in analytic sensitivity has come with a perceived loss of specificity in the most classic application – chest pain triage and the diagnosis of acute myocardial infarction (AMI). As cardiac Troponin can no longer be used as a dichotomous test, the medical field is increasingly moving towards a more granular interpretation. However, rapid rule-out/rule-in algorithms for AMI still rely on concrete thresholds for efficient triage, irrespective of the patient's comorbidities. Owing to a slightly elevated cTn value, evermore patients appear to fall into an indeterminate risk zone of diagnostic uncertainty. The reasons are manifold, spanning biological variation, analytical issues, increased plasma membrane permeability and the potential cytosolic release of cTn. This review provides a contemporary overview of the literature concerning the use of cardiac Troponin in chronic and acute cardiovascular care.

Keywords: cardiac Troponin; cardiovascular disease; acute myocardial infarction; biological variation; renal dysfunction

Key messages:

High-sensitivity cardiac Troponin assays have transformed the assessment of cardiovascular disease.

Rapid rule-out algorithms for chest pain triage have become increasingly complicated, but enable safe rule-out.

Cardiac Troponin tracks mid- to long-term risk in patients with hyperlipidaemia, heart failure and renal dysfunction.

Declaration of Interest:

The authors report no conflicts of interest pertaining to this manuscript.

'Troponitis' – is the colloquial term used by many clinicians to describe a falsely elevated (read: 'false-positive'), cardiac Troponin (cTn) result. But does such a condition actually exist? In this review we examine the use and abuse of high-sensitivity cardiac Troponin (hs-cTn) testing. By dissecting the analytic path into its components, we hope to shed light on terms such as "troponitis" and reveal they are the inevitable consequence of extreme analytic sensitivity . Further, there are numerous applications and clinical scenarios, in which high-sensitivity cardiac Troponin (hs-cTn) testing is well established and promises improved risk stratification, albeit with the caveat of some decrease in specificity and "troponitis". Firstly we will deal with the issue of analytic false-positive troponins, conditions where the assay "misfires" as a result of an analytic error.

Known pre-analytic issues usually affect cTn values through interference with the laboratory assay: haemolysis and bilirubin interference can lead to falsely low cTnT concentrations, the mechanism, however, remains largely undiscovered.(1,2) Antibodies from an endogenous source can interfere with the assay, but are felt to be comparably rare and can cause – through interference with either the cTn complex or the (hs-)cTn assay – negative or positive interference.(3,4) Biotin, which is frequently used in supplements available over-the-counter, can further interfere with biotin-streptavidin based assays – and depending on the assay formulation (competitive versus sandwich methods), this can lead to falsely low (cTn) results (5) – but rarely can also result in false-positives. Finally, skeletal muscle disease, such as most recently described by Schmid et al. (6,7), can lead to an elevated cTnT concentration (but rarely cTnI), either through cross-reaction of the assay or, less convincing, a re-expression of the cardiac isoform in diseased skeletal muscle. Other than in the latter cohort,

which should be clinically distinguishable, why do clinicians see many more patients with quantifiable cTn concentrations, who do not suffer an acute decompensation of a cardiovascular condition?

The sensitivity/specificity quagmire

Owing to greater tissue selectivity, cardiac Troponin replaced creatine kinase-MB as the biomarker of choice for the triage of patients presenting with chest pain, and the subsequent diagnosis (or rule-out) of Non-ST elevation Myocardial Infarction (NSTEMI).(8,9) Due to a slow release pattern it was, however, inherently unsuited for the early detection of myocardial injury. (10,11) To overcome this biological handicap, the sensitivity of the assays had to increase. Today's very definition of a hs-cTn assay – according to the International Federation of Clinical Chemistry and Laboratory Medicine Task Force on Clinical Applications of cardiac Bio-Markers (IFCC TF-CB) – includes 1) a CV ≤10% at the 99th centile value and 2) the ability to measure at least 50% of healthy individuals with concentrations above the assay's Limit of Detection (LoD).(12,13) As high-sensitivity assays yield quantifiable results in a majority of healthy individuals (14,15), the use of a 99th centile of a normal reference population to define a cut-off for normal vs abnormal becomes challenging in clinical day-to-day practice when it is applied to "unhealthy" patients **in an attempt to diagnose acute myocardial infarction**. The subsequent review of the literature will define the many caveats one encounters upon interpretation of cardiac Troponin results in this brave new world of high-, and imminent ultra-, sensitive assays.

Analytical precision and biological variation of cTn

For many applications of cTn in clinical practise, guidelines recommend the interpretation of baseline/presentation values plus a potential dynamic rise or fall (delta-change) of the biomarker over the clinical course.(16,17) This aids the distinction of AMI **(as cause for an**

acute myocardial injury) vs chronic causes of cTn elevation, as a single elevated level appears insufficient to make a diagnosis of the former. The interpretation of release kinetics appears justified, as a recent publication has demonstrated that the limit of detection of hs-cTn assays might be breached by necrosis of as little as 9 mg of myocardial tissue – too small to be detected by today's imaging techniques.(18) The guidelines advocate the use of either relative or absolute changes from baseline cTn **concentrations** to define a dynamic change, whereas the latter appears to be more accurate in the diagnosis of AMI (19) and is endorsed in the 2015 ESC 0/1h NSTEMI rule-out pathway.(17) The recommended delta-change values are comparably small (e.g. 3 ng/L for hs-cTnT (Elecsys), 2 ng/L for hs-cTnI (Architect)). This might be problematic for two reasons: 1) **cTnI concentrations appear to vary randomly over a 24h period, with a constant CV_I (coefficient of variation within-subject) of 8-9% for all time intervals, irrespective of underlying renal function (20,21) – whereas** hs-cTnT **follows a** marked diurnal variation, characterised by a mean difference of 4 ng/L between morning and evening samples in healthy volunteers **(thus unlikely to affect delta-change values in clinical practise)(21)**; 2) within-subject coefficient of variation values (CV_I) range from 3.4-24% for hs-cTnI (Architect) and 1.2-48.2% for hs-cTnT (Elecsys) even during short-term repeats.(22–24) In summary, this might affect the number of patients that benefit from the use of small delta-change values, given that most hs-cTn assays yield a CV_A of ~20% below the 99th centile – precisely the concentration range where the delta-change values are used to triage the individual with chest pain (see also Kavsak et al. (25)). Reassuringly however, this will tend to yield false-positives, rather than false-negatives, as only patients with low baseline cTn without dynamic delta-change values qualify for rule-out.

Chest pain triage and diagnosis of Acute Myocardial Infarction

When cardiac Troponin was an insensitive assay, it was impossible to quantify the *normal* distribution in a reference population. Thus, the 99th centile of a healthy reference-population was defined as a cut-off for an elevated result.(8,26) Arguably, the most common use of cardiac Troponin assays to date lies in chest pain triage – their relative sensitivity is unmatched by cardiac imaging techniques, which are incapable of detecting the small volumes of myocardial necrosis that will trigger a troponin rule-in decision.(18) Guidelines by the American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC) endorse the use of hs-cTn, but frequently advocate decision limits which are widely-spaced around the 99th centile for triage purposes.(16,17) This is to limit the downstream effect of using hs-cTn assays, which include (i) a 2-fold increase of detection of type 2 AMI, (ii) ~20% relative increase in detection of type 1 AMI and (iii) 'elevations up to 3-fold the upper reference limit (URL), which,…may be associated with a broad spectrum of conditions'. (17) As the main purpose of these guidelines is the selection of patients with type 1 myocardial infarction (a plaque rupture event), triage focusses on risk-stratification into (safe) rule-out, and rule-in categories (with high PPV for AMI).

In addition to guideline-endorsed pathways, there are a number of different strategies to facilitate safe and rapid rule-out – Mueller et al. have provided a summary in 2017 (27), and there are alternative approaches as used in the HighSTEACS and the ICare-ACS trials.(28–30) Most pathways facilitate safe rule-out of AMI (with a Negative Predictive Value ≥99%), but with variable 'triage efficacy' – as determined by the number of patients which remain in an indeterminate 'observe' zone after applying the algorithm. Several publications have reported on the variable effectiveness of e.g. the ESC algorithm in clinical practice – many patients have to undergo a second blood draw in an attempt to increase efficiency of triage by

migration from the ‘observe’ category of diagnostic uncertainty to either rule-out or -in. As few as 20-30% of patients benefit from immediate (i.e. on first blood draw) rule-out/-in using the cut-offs published.(31–33) In some healthcare environments, this poses logistical challenges for the Emergency Department – in an increasing number of countries, such as the US and the UK, performance targets concerning Emergency Care provision demand rapid triage, with an admit or discharge decision required within four hours of arrival to hospital.(34–36) In these countries, approaches that increase the number of patients eligible for direct rule-out (i.e. after a single blood test) would decrease pressures on strained resources. Shah et al. have demonstrated an increase in eligible patients with no significant reduction in safety (based on NPV >99%) by increasing the rule-out threshold using hs-cTnI (Abbott; from ESC at 2 ng/L) to 5 ng/L.(29) As any cut-off is assay-dependent, caution must be exercised when applying published algorithms to local practices.

Using the ESC 0/1h pathway, 24-50% of patients remain in the ‘observe’ zone despite a second blood draw (table 1).(33,37) The cohorts studied are not homogenous, most simply demonstrated by the variable prevalence of AMI, which fluctuates between 4% in US and >17% in European populations.(38) The patients remaining in the ‘observe’ zone tend to be older, with pre-existing coronary artery disease, and 15% of this subgroup are ultimately diagnosed with AMI**. While Nestelberger et al have described the patients in the ‘observe’ zone as** a heterogenous group with a rate of survival at 2 years (86%) **similar to** the ‘rule-in’ cohort **(37), a recent analysis by Twerenbold et al quotes overall mortality after 1 year at 5.7-7.2%, depending on hs-cTn assay used for risk stratification (vs 8-10.4% in the rule-in group).(39) The discrepancy might stem from a difference in length of follow-up and number of patients recruited, but emphasises that these patients are not at low risk of morbidity and mortality**. An overview of the reported proportion of

patients in the ‘observe’ zone from different studies/cohorts is provided in tables 1-3.(36,37,48–57,40,58,41–47)

One further concern affects the efficacy of hs-cTn pathways in patients with renal dysfunction – not only are the median cTn **concentrations** higher this group, but this population is also at increased risk of cardiovascular events.(59,60) Twerenbold et al. demonstrated that the prevalence of NSTEMI was substantially higher in patients with renal dysfunction (31% vs 13%); while safety of the 0/1h ESC pathway (as defined by sensitivity) was unaffected, triage efficacy suffered as only 18% of patients qualified for rule-out (compared to 68% in patients without underlying renal disease) – findings corroborated by Miller-Hodges et al.(46,61)

In summary, hs-cTn assays enable safe rule-out (with NPV ≥99%) employing a number of different algorithms with varying degrees of overall efficacy. **The application of rapid rule-in/rule-out algorithms using 0/1h-repeat sampling accelerate the diagnostic pathway when compared to the use of contemporary cTn assays mandating 6-12 hour repeat testing. However,** the algorithms for chest pain triage have become more complicated as more patients have quantifiable cTn **concentrations**, and conditions affecting baseline cardiovascular risk such as underlying renal dysfunction contribute significantly to a higher number of patients unsuitable for rule-out of AMI using very low hs-cTn **concentrations**. Furthermore, clear guidance is currently lacking to determine the most appropriate follow-up investigation to further risk-stratify patients with elevated cTn **concentrations** that do not fulfil rule-in criteria. In the acute setting, hs-cTn is therefore most useful when (nearly undetectably) low, or significantly elevated – in between, there remains a great amount of uncertainty, which to date can only be addressed with thorough clinical assessment and appropriate investigations on a case-by-case basis.

Heart failure

Detectable concentrations of circulating troponins below and above the 99th percentiles of healthy populations are commonly found in patients with heart failure outside the context of an acute coronary syndrome. Reports on the incidence of troponin elevation in patients with heart failure vary depending on the population, the severity of heart failure, the sensitivity of assay used, and the cut-off points.(62)

High sensitivity troponin assays allow the detection of circulating troponin in almost all patients with heart failure (63,64), with **concentrations** above the 99th percentile found in the majority of patients with chronic (64,65), and nearly all patients with acute heart failure.(63,66)

In those without clinical, electrocardiographic or imaging evidence of Type 1 MI (the classic plaque-rupture event), causes of troponin elevation remain elusive and speculative in the majority of cases. Suggested mechanisms include myocardial injury by inflammatory cytokines or oxidative stress, hibernating myocardium, apoptosis, increased plasma membrane permeability of viable injured cells (62), and stretch related mechanisms in viable non-injured cardiomyocytes mediated by integrins.(67)

Whereas the therapeutic implications of identifying troponin elevation in the context of type 1 MI compounded by heart failure is well-described, it has yet to be explored and established for all other causes. Irrespective of the underlying pathophysiology, troponin elevation in patients with heart failure has significant prognostic value: Numerous studies have reported a strong direct association between elevated troponin and the incidence of mid- to long-term adverse cardiovascular events, including all-cause mortality, cardiovascular death, worsening heart failure during index admission, rehospitalisation and cardiac transplantation, in both ischemic and non-ischemic heart failure.(63,64,75–79,65,68–74)

Studies have also shown that serial testing of cardiac troponins in patients with decompensated and chronic heart failure may provide more robust prognostic information than a single measurement, as patients with increasing troponin **concentrations** have significantly worse outcomes than those with stable or decreasing values.(63,64)

Additionally, minimally elevated troponins in otherwise healthy individuals (e.g. without pre-existing ischaemic heart disease) may predict future development of heart failure.(80)

In summary, beyond the context of acute myocardial infarction, and irrespective of the aetiology of heart failure, elevated cTn is an independent predictor of adverse outcomes in patients with heart failure. The impact on treatment and follow up is yet to be established in clinical trials.

Renal failure

Accurate interpretation of elevated cTn **concentrations** in the presence of renal disease is an everyday challenge and requires careful consideration of the clinical context. There are several contributing factors, including the increased likelihood of atypical presentations in this group (81) and the presence of chronically detectable troponin **concentrations** below and above the 99th percentile in some patients with chronic renal disease. Furthermore, the exact pathophysiology of chronic stable cTn elevation, and whether this is due to reduced renal elimination or increased cardiac release caused by coexistent coronary artery disease and/or accumulating toxins, remain unclear.(82)

As described above, significant heterogeneity exists between studies reporting on the diagnostic accuracy of hs-cTn in patients with renal disease and suspected myocardial infarction. Patients with end-stage renal failure and patients on dialysis were under-represented in most studies, and caution is required extrapolating overall results, to this underrepresented subgroup. In summary, the safety of contemporary troponin-based

diagnostic approaches is high, but the specificity of rule-in and overall efficacy are significantly decreased. Adjusting the cut-off thresholds did not improve their diagnostic performance.(61) However, there is a clear prognostic signal: Short- and long-term risk (for death or a subsequent cardiovascular event) for patients with renal disease and elevated troponins, is twice as high as for those without.(46)

Stable coronary artery disease

High sensitivity troponin assays allow the detection of circulating troponins in nearly all patients with stable coronary artery disease (CAD).(83–85) The cause for higher median **concentrations** of cTn in this cohort over 'healthy' individuals without underlying CAD is not yet identified: apoptosis, cardiomyocyte turnover, strain, increased cardiac mass and subclinical plaque rupture (86) have all been suggested. In patients with stable CAD referred for elective coronary angiography, a direct association between elevated circulating Troponin **concentrations** and the extent of coronary atherosclerosis and high-risk plaque phenotypes (assessed with intracoronary IVUS in a non-culprit coronary artery) has been demonstrated.(86)

As observed in patients with renal dysfunction and heart failure, higher cTn values seem to translate into a worse prognosis even in the stable ambulatory patient. The magnitude of cTn elevation independently predicts risks of cardiovascular death and heart failure in patients with stable CAD.(84) The incremental change in troponin **concentrations** on serial testing also appears to be associated with a higher risk of adverse events than stable or decreasing trends.(87)

Lowering troponin concentrations in asymptomatic individuals–a worthy goal?

Several studies and post-hoc analyses highlighted the possibility of drug-induced modification of cTn release and thus a potential effect on future risk and prognosis in select groups, in a variety of settings.

However, the debate continues about the mechanism by which drugs can modify cTn release and thus potentially lower future risk in a wide spectrum of cardiac disease. One recent proof-of-concept study in otherwise asymptomatic individuals is worth highlighting: would modifying cTn **concentrations** in patients without **established** coronary artery disease **or heart failure** affect their cardiovascular outcomes?

WOSCOPS **(West of Scotland Coronary Prevention Study)** randomized men with raised low-density lipoprotein cholesterol (LDL) and no history of myocardial infarction to pravastatin 40 mg once daily or placebo for 5 years.(88,89) Ford et al. measured cTnI concentration with a high-sensitivity assay at baseline and at 1 year in 3,318 participants **of WOSCOPS** to establish whether cTnI **values** can be modified with statin therapy and whether the change in cTnI **concentration** is an independent predictor of future coronary risk, irrespective of cholesterol lowering. Indeed, cTnI **concentrations** fell in a presumed response to statin therapy, and the change in troponin concentration at 1 year was a strong predictor of nonfatal myocardial infarction or death from coronary heart disease. The additive decrements in future cardiovascular risk were independent of LDL cholesterol lowering.(89)

However, only modest statin induced cTnI reduction was reported in stable patients with previous MI or unstable angina receiving pravastatin 40 mg in another prospective study.(87) Overall, the exact mechanism by which statin therapy **might** reduce cTn release is unclear; similarly, the underlying mechanism as to why statin-induced cTn reduction modifies future

risk, regardless of cholesterol lowering is also unexplained. **Irrespective of the mechanism, lowering cTn concentrations appears to be associated with an improved prognosis. Clearly, there is an ongoing need for robust data to determine underlying mechanisms and study the effects of different drugs in asymptomatic individuals for the purpose of primary prevention.**

Troponin release with exercise

A significant increase in the serum concentrations of cTn after exercise, in otherwise healthy and asymptomatic individuals, is reported in numerous studies.(87,90–97) But the prevalence of cTn elevation among the study participants varies depending on the cohort, the type and intensity of exercise, and the assay used. The magnitude of cTn release did not correlate with the presence of conventional cardiac risk factors, but with younger age (98,99), less training and experience (90,98) and increased intensity of exercise.(94,97,99) Further, cTn elevation was associated with an alteration in cardiac function demonstrated on Cardiac Magnetic Resonance Imaging (cMRI). However, the findings varied in terms of anatomical location and degree of dysfunction across studies (88,90–93,100–102), and there was no evidence of associated myocardial oedema or fibrosis on cMRI (93,103–105). This supports the hypothesis that the cTn increase is likely due to a benign cytosolic release, secondary to increased cellular permeability, rather than a sinister ischaemic insult.(87,91,96) Nevertheless, the clinical significance of exercise-induced rises in cTn concentration remains unclear. In the absence of accompanying symptoms and signs of myocardial infarction or exercise induced myocarditis, post-exercise cTn rise should be interpreted carefully. Although highly increased cTn following exercise might suggest sub-clinical coronary artery disease in otherwise healthy individuals (95), prognostic value and possible preventive therapies are yet to be identified in this group.

Conclusions

Cardiac Troponin has transformed the provision of acute cardiac care – most notably, in the triage of patients presenting with chest pain, where novel rule-in/-out strategies speed up identification of individuals suitable for early discharge, and enhance the diagnosis of myocardial infarction. Owing to greater analytic sensitivity, the field has, however, became more blurred, and some might mourn the perceived loss of specificity in the diagnosis of AMI. This can be, to a certain degree, overcome by using decision thresholds for rule-in of AMI which are many-fold higher than the respective 99th centile of the assay used – which invariably achieves higher specificity & PPV than a simple dichotomous threshold (such as the 99th centile). As we discuss in this review, this results in a variable proportion of patients assigned to an 'observe' zone, where diagnostic clarity is lost and thorough clinical assessment, the use of imaging modalities and re-testing are required to guide further treatment. The former – the clinical assessment – is enhanced by the knowledge that hs-cTn assays yield a quantifiable result in most patients seen in daily clinical practice: in those with heart failure, renal dysfunction, stable coronary artery disease, following relatively intense exercise; and in rare cases due to analytical (im-)precision and biological variation. The physician should be comfortable with the interpretation of cardiac biomarkers in a similar fashion as they understand reference ranges for blood counts, so deriving most benefit from increased sensitivity, accelerated decision pathways and enhanced risk prediction. The latter underlines the incredible value high-sensitivity assays bring to the diagnostic arsenal: an elevation in the cardiac biomarker profile is meaningful as it tracks risk for future morbidity and mortality. Whilst we need to strive for a better understanding of the exact mechanisms that underlie a 'chronically elevated' cTn **concentration**, such a finding alone should probably prompt a comprehensive cardiovascular workup, to exploit all opportunities in modifying future risk using established therapies that impart prognostic benefit. But, the

myth of ‘false-positives’ can – and should in most cases – be laid to rest, to be replaced by an understanding of a true biological signal that cTn offers.

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Ref	*Patient category after 0/1h hs-cTn*								*MI prevalence by category*			*Comments/Assay*
	Study/Centre	**n**	**Obs (%)**	**RO (%)**	**RI (%)**	**Age**	**CAD (%)**	**MI (%)**	**Obs (%)**	**RO (%)**	**RI (%)**	
39	APACE Multicentre - IT, CH, ES	1656	24.1	59.5	16.4	60 [49-74]	33.3	17.3	18	0.13	78.24	A1
40a	Multicentre - NZ, CA, AU	2222	22.7	64.1	13.1	59 (SD 14)	*	9.7	9.5	0.49	63.36	a = hs-cTnT cohort; A1
40b	Multicentre - NZ, CA, AU	2222	31.8	54.2	14.0	59 (SD 14)	*	9.7	9.5	0.25	68.06	b = hs-cTnI cohort; A2
41	APACE Multicentre	436	23.2	59.4	17.4	63 [50-75]	36	17	8	0.00	84.21	Validation cohort; A1
42	TRAPID-AMI Multicentre	1282	22.2	63.4	14.4	62 [50-74]	36.9	17	22.5	0.86	77.17	A1
45a	APACE Multicentre European cohort	2767	18.5	67.9	13.3	58 [47-70]	29	13	15	0.16	77.11	Using data set A from trial with normal renal function; A1
45b	APACE Multicentre European cohort	487	48.7	18.1	33.3	79 [73-84]	57	31	11	0.00	76.54	Using data set A from trial with abnormal renal function; A1
45c	APACE Multicentre European cohort	2504	23.9	57.8	18.3	58 [47-70]	29	13	15	0.48	60.70	Using data set B from trial with normal renal function; A2
45d	APACE Multicentre European cohort	445	46.5	17.3	36.2	79 [73-84]	58	31	13	2.60	70.81	Using data set B from trial with abnormal renal function; A2

51	Multicentre – JP, TW	413	27.8	41.4	30.8	72 [59-81]	24.5	13.8	17.4	0.00	33.07	exclusively Asian population; A1

Table 1 – Overview of studies modelled on ESC 0/1h rule-out/rule-in algorithm; Ref = Reference as per quotation in main text; Obs = Observation group; RO = Rule-Out group; RI = Rule-In group; Age quoted as Median [IQR] unless stated otherwise; CAD = Coronary Artery Disease; MI = Myocardial Infarction; IT = Italy; CH = Switzerland; ES = Spain; NZ = New Zealand; CA = Canada; AU = Australia; JP = Japan; TW = Taiwan; SE = Sweden; A1 = Elecsys hs-cTnT; A2 = Architect hs-cTnI

Ref	***Patient category after 0/2h algorithm***								***MI prevalence by category***			*Comments/Assay*
	Study/Centre	**n**	**Obs (%)**	**RO (%)**	**RI (%)**	**Age**	**CAD (%)**	**MI (%)**	**Obs (%)**	**RO (%)**	**RI (%)**	
53a	APACE Multicentre	1148	24.2	59.5	16.3	62 [51-74]	36	16	15	0.15	78.07	Derivation cohort; A1
53b	APACE Multicentre	517	14.5	77.8	7.7	54 [45-65]	26	9.1	15	0.50	85.00	Validation cohort; A1
54a	APACE Multicentre - European cohort	1435	27.2	56.0	16.7	62 [49-74]	35	17	14	0.25	75.83	Derivation cohort 0/2h algorithm; A2
54b	APACE Multicentre - European cohort	1194	27.4	59.9	12.7	61 [50-73]	21	13	9	0.28	82.24	Validation cohort 0/2h algorithm; A3
55	ADAPT cohort - AU, NZ	1624	31.0	58.7	10.3	60.5 (SD 15)	45.8	13.9	14.5	0.73	86.31	Biomarker + ECG algorithm; A3
57	Multicentre - UK	722	25.1	58.4	16.5	58.8 [51-69]	*	13.7	4.4	0.24	58.82	A1
56	Multicentre - SE	605	25.5	61.8	12.7	65 [54-75]	24.9	14.2	10.4	0.80	87.01	Derivation cohort; A4

Table 2 – Overview of studies using 0/2h rule-out/rule-in algorithm; Ref = Reference as per quotation in main text; Obs = Observation group; RO = Rule-Out group; RI = Rule-In group; Age quoted as Median [IQR] unless stated otherwise; CAD = Coronary Artery Disease; MI = Myocardial Infarction; IT = Italy; CH = Switzerland; ES = Spain; NZ = New Zealand; CA = Canada; AU = Australia; JP = Japan; TW = Taiwan; SE = Sweden; A1 = Elecsys hs-cTnT; A2 = Architect hs-cTnI; A3 = Vista hs-TnI; A4 = Vidas hs-cTnI

Ref	*Patient category after algorithm*							*MI prevalence by category*			*Comments/Assay*
	Study/Centre	**n**	**Obs (%)**	**RO (%)**	**RI (%)**	**Age**	**CAD (%)**	**MI (%)**	**Obs (%)**	**RO (%)**	**RI (%)**	
48	APACE Multicentre	649	23.0	64.7	12.3	62 [50-74]	35	17	14.8	1.43	76.25	Validation cohort; A5
46	Multicentre - AU, NZ (ADAPT, EDACS)	2537	43.4	42.9	13.8	62 [49-75]	35	18	10.0	0.46	83.95	Combination A1+A2 at presentation; validation cohort
43	APACE Multicentre - IT, CH, ES	905	30.5	50.5	19.0	62 [50-74]	37	19	13.0	0.44	76.00	Validation cohort; 0h hs-cTnI <5 ng/L for RO, delta 1h ≥6 ng/L for RI; A2
44	APACE Multicentre - IT, CH, ES	750	29.9	57.1	13.1	60 [48-72]	32	13	13.0	0.00	70.00	Validation cohort; A3
36	Single centre - St Thomas' Hospital, UK	4644	51.9	40.4	7.7	54 [41-70]	*	21.2	*	*	*	Presentation sample (0h) only; A1
47a	APACE Multicentre - CH, IT, PL, ES, CZ	1416	63.5	23.4	13.1	62 (SD 16)	36	17	11.0	0.00	81.08	A1 cohort with chest pain for ≥3 hours; presentation (0h) sample only
47b	APACE Multicentre - CH, IT, PL, ES, CZ	1397	70.5	13.2	16.3	63 (SD 16)	36	17	11.0	0.00	71.49	A2 cohort with chest pain for ≥3 hours; presentation (0h) sample only
49a	Multicentre - CA	1137	35.1	52.5	12.4	66.6 (SD 16.3)	36	11.7	14.3	1.68	46.81	taken from Algorithm 4 data, modified ESC algorithm; A1
49b	Multicentre - CA	1137	47.6	44.3	8.1	66.6 (SD 16.3)	36	11.7	11.5	0.79	72.83	taken from Algorithm 4 data, modified ESC algorithm; A2

50	Single centre - Manchester Royal Infirmary, UK	703	42.1	27.7	30.2	58.6 (SD 14.3)	23.8	18	6.4	0.00	52.36	Using 3-14 ng/L as observe zone for 0/1h cTn; A1; additional computer model

Table 3 – Overview of studies using modified rapid rule-out/rule-in algorithms; Ref = Reference as per quotation in main text; Obs = Observation group; RO = Rule-Out group; RI = Rule-In group; Age quoted as Median [IQR] unless stated otherwise; CAD = Coronary Artery Disease; MI = Myocardial Infarction; IT = Italy; PL = Poland; CH = Switzerland; ES = Spain; NZ = New Zealand; CA = Canada; AU = Australia; JP = Japan; TW = Taiwan; SE = Sweden; A1 = Elecsys hs-cTnT; A2 = Architect hs-cTnI; A3 = Vista hs-TnI; A4 = Vidas hs-cTnI; A5 = ADVIA Centaur s-cTnI; * Data not available